The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ European Patent Office

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only

Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION

Applicant's or agent's file reference: PCT-58

International application No.	International filing date *(day/month/year)*	(Earliest) Priority date *(day/month/year)*
PCT/ES99/00375	23 November 1999	24 November 1998

Title of invention: "TGF 1-INHIBITOR PEPTIDES"

Box No. II APPLICANT(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

INSTITUTO CIENTIFICO Y TECNOLOGICO DE NAVARRA, S.A.
Avda. Pío XII, 53
31008 Pamplona
Spain

Telephone No.:

Facsimile No.:

Teleprinter No.:

State *(that is, country)* of nationality: SPAIN

State *(that is, country)* of residence: SPAIN

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

EZQUERRO SAENZ, Ignacio José
Travesía Monasterio de Velate, 2-3º A
Pamplona
Spain

State *(that is, country)* of nationality: SPAIN

State *(that is, country)* of residence: SPAIN

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

LASARTE SAGASTIBELZA, Juan José
Avda. de Guipúzcoa, 24-3º
Berriozar
Spain

State *(that is, country)* of nationality: SPAIN

State *(that is, country)* of residence: SPAIN

[X] Further applicants are indicated on a continuation sheet.

International application No.
PCT/ES99/00375

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

PRIETO VALTUEÑA, Jesús
C/ Tudela, 22-4º
Pamplona
Spain

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
SPAIN	SPAIN

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

BORRAS CUESTA, Francisco
C/ Montecampamento, 37-3ºA, Mendillorri
Pamplona
Spain

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

☐ Further applicants are indicated on another continuation sheet.

International application No.
PCT/ES99/00375

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is [X] agent [ ] common representative

and [X] has been appointed earlier and represents the applicant(s) also for international preliminary examination.

[ ] is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

[ ] is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

ELZABURU, Alberto
Miguel Angel, 21
28010 Madrid
Spain

Telephone No.: 91 700 94 00

Facsimile No.: 91 319 38 10

Teleprinter No.:

[ ] **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination **to start on the basis of:**

[X] the international application as originally filed

the description [ ] as originally filed
[ ] as amended under Article 34

the claims [ ] as originally filed
[ ] as amended under Article 19 (together with any accompanying statement)
[ ] as amended under Article 34

the drawings [ ] as originally filed
[ ] as amended under Article 34

2. [ ] The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. [ ] The applicant wishes the start of the international preliminary examination **to be postponed** until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English

[ ] which is the language in which the international application was filed.

[ ] which is the language of a translation furnished for the purposes of international search.

[ ] which is the language of publication of the international application.

[X] which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box N . V ELECTION OF STATES

The applicant hereby **elects all eligibl States** *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes **not to elect:**

See Notes to the demand form

International application No.
PCT/ES99/00375

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

				For International Preliminary Examining Authority use only	
				received	not received
1. translation of international application	:	82	sheets	☐	☐
2. amendments under Article 34	:		sheets	☐	☐
3. copy (or, where required, translation) of amendments under Article 19	:		sheets	☐	☐
4. copy (or, where required, translation) of statement under Article 19	:		sheets	☐	☐
5. letter	:	1	sheets	☐	☐
6. other *(specify)* declaration statement on ~~sequence listing~~	:	1	sheets	☐	☐

The demand is also accompanied by the item(s) marked below:

1. [X] fee calculation sheet
2. [ ] separate signed power of attorney
3. [ ] copy of general power of attorney; reference number, if any:
4. [ ] statement explaining lack of signature
5. [X] nucleotide and or amino acid sequence listing in computer readable form
6. [X] other *(specify)*: Additional representatives

B x No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

Alberto de Elzaburu
Por Poder

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:
2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):
3. [ ] The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. [ ] The applicant has been informed accordingly.
4. [ ] The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.
5. [ ] Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

See Notes to the demand form

CHAPTER II

PCT

FEE CALCULATION SHEET

Annex to the Demand for international preliminary examination

International application No. PCT/ES99/00375	For International Preliminary Examining Authority use only
Applicant's or agent's file reference PCT-58	Date stamp of the IPEA

Applicant: INSTITUTO CIENTIFICO Y TECNOLOGICO DE NAVARRA, S.A.

Calculation of prescribed fees

1. Preliminary examination fee	EUR 1.533	P
2. Handling fee *(Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.)*	EUR 148	H
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box.....	EUR 1.681	TOTAL

Mode of Payment

[X]	authorization to charge deposit account with the IPEA (see below)	[ ]	cash
[ ]	cheque	[ ]	revenue stamps
[ ]	postal money order	[ ]	coupons
[ ]	bank draft	[ ]	other *(specify)*:

Deposit Account Authorization *(this mode of payment may not be available at all IPEAs)*

The IPEA/ EPO [X] is hereby authorized to charge the total fees indicated above to my deposit account.

[X] *(this check-box may be marked only if the conditions for deposit accounts of the IPEA so permit)* is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.

28120008	19th June 2000	Alberto de Elzaburu For Poder
Deposit Account Number	Date *(day/month/year)*	Signature

See Notes to the fee calculation sheet

Mr. Alberto de Elzaburu, as representative of INSTITUTO CIENTIFICO Y TECNOLOGICO DE NAVARRA, S.A., in the prosecution of PCT application for "TGFβ1-INIHIBITOR PEPTIDES",

DECLARES

that, in virtue of Art. 13 ter of the PCT Rules, the sequence listing attached herewith in computer readable system, does not include which goes beyond the disclosure in the international application as filed.

I sign the present declaration in Madrid, Spain, this 19th day of June 2000.

Alberto de Elzaburu
Por Poder

ADDITIONAL REPRESENTATIVE(S)

ADDITIONAL SHEET PERTAINING TO INTERNATIONAL PATENT APPLICATION IN THE NAME OF INSTITUTO CIENTIFICO Y TECNOLOGICO DE NAVARRA, S.A., CORRESPONDING TO INTERNATIONAL PATENT APPLICATION N° PCT/ES99/00375 OF 24 NOVEMBER 1999.

ADDITIONAL REPRESENTATIVES

Enrique Armijo

Argimiro Cadenas

ALL WITH PROFESSIONAL PRACTICE AT MIGUEL ANGEL Nº 21, MADRID, SPAIN

WO 00/31135
PCT/ES99/00375

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:
DE ELZABURU, Alberto
Miguel Angel, 21
E-28010 Madrid
ESPAGNE

ELZABURU
12 DEC 00 069377

JL

ACH

Date of mailing (day/month/year)	
02 June 2000 (02.06.00)	
Applicant's or agent's file reference	**IMPORTANT NOTICE**
PCT-58	

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/ES99/00375	23 November 1999 (23.11.99)	24 November 1998 (24.11.98)

Applicant
INSTITUTO CIENTIFICO Y TECNOLOGICO DE NAVARRA, S.A. et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AU,CN,JP,KP,KR,MA,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AE,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CR,CU,CZ,DE,DK,DM,EA,EE,EP,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,ZA,ZW
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   02 June 2000 (02.06.00) under No. WO 00/31135

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer
J. Zahra

Telephone No. (41-22) 338.83.38

PETITORIO PCT PCT-58

Original (para **PRESENTACION**) - impreso el 22.11.1999 03:15:47 PM

0	**Para uso de la Oficina receptora únicamente**	
0-1	Solicitud internacional No..	
0-2	Fecha de presentación internacional	
0-3	Nombre de la Oficina receptora y "Solicitud Internacional PCT"	

0-4	**Formulario - PCT/RO/101 Petitorio PCT**	
0-4-1	Preparado usando	PCT-EASY Version 2.90 (actualizado el 15.10.1999)
0-5	**Petición** El abajo firmante solicita que la presente solicitud internacional sea procesada de acuerdo con el Tratado de Cooperación en materia de Patentes	
0-6	**Oficina receptora (indicada por el solicitante)**	Oficina Española de Patentes y Marcas (RO/ES)
0-7	**Referencia al expediente del solicitante o del mandatario**	PCT-58
I	**Título de la invención**	PEPTIDOS INHIBIDORES DE TGF BETA 1
II	**Solicitante**	
II-1	Esta persona es:	solicitante únicamente
II-2	Solicitante para	todos los Estados designados salvo los Estados Unidos de América
II-4	Nombre	INSTITUTO CIENTIFICO Y TECNOLOGICO DE NAVARRA, S.A.
II-5	Dirección:	Avda. Pío XII, 53 31008 Pamplona España
II-6	Estado de nacionalidad	ES
II-7	Estado de domicilio	ES
III-1	**Solicitante e/o inventor**	
III-1-1	Esta persona es:	solicitante e inventor
III-1-2	Solicitante para	Estados Unidos de América únicamente
III-1-4	Nombre (APELLIDOS, Nombre)	EZQUERRO SAENZ, Ignacio José
III-1-5	Dirección:	Travesía Monasterio de Velate, 2-3° A Pamplona España
III-1-6	Estado de nacionalidad	ES
III-1-7	Estado de domicilio	ES

PETITORIO PCT

PCT-58

Original (para **PRESENTACION**) - impreso el 22.11.1999 03:15:47 PM

III-2	**S licitante e/ inventor**	
III-2-1	Esta persona es:	solicitante e inventor
III-2-2	Solicitante para	Estados Unidos de América únicamente
III-2-4	Nombre (APELLIDOS, Nombre)	LASARTE SAGASTIBELZA, Juan José
III-2-5	Dirección:	Avda. de Guipúzcoa, 24-3° Berriozar España
III-2-6	Estado de nacionalidad	ES
III-2-7	Estado de domicilio	ES
III-3	**Solicitante e/o inventor**	
III-3-1	Esta persona es:	solicitante e inventor
III-3-2	Solicitante para	Estados Unidos de América únicamente
III-3-4	Nombre (APELLIDOS, Nombre)	PRIETO VALTUEÑA, Jesús
III-3-5	Dirección:	Tudela, 22-4° Pamplona España
III-3-6	Estado de nacionalidad	ES
III-3-7	Estado de domicilio	ES
III-4	**Solicitante e/o inventor**	
III-4-1	Esta persona es:	solicitante e inventor
III-4-2	Solicitante para	Estados Unidos de América únicamente
III-4-4	Nombre (APELLIDOS, Nombre)	BORRAS CUESTA, Francisco
III-4-5	Dirección:	Montecampamento, 37-3° A, Mendillorri Pamplona España
III-4-6	Estado de nacionalidad	ES
III-4-7	Estado de domicilio	ES
IV-1	**Mandatario o representante común; o dirección para la correspondencia** La persona identificada a continuación se designa/ha sido designada para actuar en nombre del/de los solicitante(s) ante las administraciones internacionales competentes como:	mandatario
IV-1-1	Nombre (APELLIDOS, Nombre)	ELZABURU, Alberto de
IV-1-2	Dirección:	Miguel Angel, 21 28010 Madrid España
IV-1-3	No. de teléfono	917009400
IV-1-4	No. de telefacsímile	913193810
IV-1-5	Correo electrónico	elzaburu@elzaburu.es

PETITORIO PCT

PCT-58

Original (para **PRESENTACION**) - impreso el 22.11.1999 03:15:47 PM

V	**Designación de Estados**	
V-1	Patente regional (otros tipos de protección o de tramitación, si es posible hacerlo, están indicados entre paréntesis a continuación de la(s) designación(es) correspondiente(s))	AP: GH GM KE LS MW SD SL SZ TZ UG ZW y cualquier otro Estado contratante del Protocolo de Harare y del PCT EA: AM AZ BY KG KZ MD RU TJ TM y cualquier otro Estado contratante del Convenio sobre la Patente Euroasiática y del PCT EP: AT BE CY CH&LI DE DK ES FI FR GB GR IE IT LU MC NL PT SE y cualquier otro Estado contratante del Convenio sobr la Patente Europea y del PCT OA: BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG y cualquier otro Estado que sea Estado miembro de la OAPI y que sea un Estado contratante del PCT
V-2	Patente nacional (otros tipos de protección o de tramitación, si es posible hacerlo, están indicados entre paréntesis a continuación de la(s) designación(es) correspondiente(s))	AE AL AM AT AU AZ BA BB BG BR BY CA CN CR CU CZ CH&LI DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
V-5	**Declaración de designación precautoria** Además de las designaciones efectuadas en los puntos V-1, V-2 y V-3, el solicitante efectuará también, envirtud de la Regla 4.9.b), todas las designaciones que estén permitidas con arreglo al PCT, salvo la(s) designación(es) del(de los) Estado(s) indicado(s) en el punto V-6 a continuación. El solicitante declara que esas designaciones adicionales están sujetas a confirmación y que cualquier designación que no se confirme antes de que expiren los 15 meses a partir de la fecha prioritaria se considerará retirada por el solicitante al expirar dicho plazo.	
V-6	**Exclusión de las designaciones precautorias**	NINGUNA
VI-1	**Reivindicación de prioridad de una solicitud nacional anterior**	
VI-1-1	Fecha de presentación	24 Noviembre 1998 (24.11.1998)
VI-1-2	Número	9802465
VI-1-3	País	ES
VI-2	**Petición de documento de prioridad** Se ruega a la Oficina receptora que prepare y transmita a la Oficina Internacional una copia certificada de la(s) solicitud(es) anterior(es) identificada(s) supra com punto(s):	VI-1
VII-1	**Administración encargada d la búsqu da internaci nal legida**	Oficina Española de Patentes y Marcas (ISA/ES)

PETITORIO PCT

PCT-58

Original (para **PRESENTACION**) - impreso el 22.11.1999 03:15:47 PM

VIII	Lista de verificación	número de hojas	fichero(s) el ctrónico(s) adjunto(s)
VIII-1	Petitorio	4	-
VIII-2	Descripción (excluida la parte correspondiente a la relación de secuencias)	47	-
VIII-3	Reivindicaciones	2	-
VIII-4	Resumen	1	resumen_pct58.txt
VIII-5	Dibujos	28	-
VIII-6	Relación de secuencias, como parte de la descripción	3	-
VIII-7	TOTAL	85	
	Elementos de acompañamiento	documento(s) en papel adjunto(s)	fichero(s) electrónico(s) adjunto(s)
VIII-8	Hoja de cálculo de tasas	✓	-
VIII-9	Poder separado firmado		-
VIII-15	Relación de una secuencia de nucleótidos y/o aminoácidos en formato legible por ordenador		disquete separado
VIII-16	Disquete PCT-EASY	-	disquete
VIII-18	**Figura de los dibujos que debe acompañar el resumen**		
VIII-19	**Idioma de presentación de la solicitud internacional**	español	
IX-1	**Firma del solicitante o del mandatario**		
IX-1-1	Nombre (APELLIDOS, Nombre)	ELZABURU, Alberto de P.P.	

PARA USO DE LA OFICINA RECEPTORA UNICAMENTE

10-1	**Fecha efectiva de recepción de la pretendida solicitud internacional**	
10-2	**Dibujos:**	
10-2-1	Recibido	
10-2-2	No recibido	
10-3	**Fecha efectiva de recepción, rectificada en razón de la recepción ulterior pero dentro del plazo, de documentos o de dibujos que completan la pretendida solicitud internacional**	
10-4	**Fecha de recepción, dentro del plazo, de las correcciones solicitadas según el Artículo 11(2) del PCT**	
10-5	**Administración encargada de la búsqueda internacional**	ISA/ES
10-6	**Transmisión de la copia para la búsqueda diferida hasta que se pague la tasa de búsqueda**	

PARA USO DE LA OFICINA INTERNACIONAL UNICAMENTE

11-1	**Fecha de recepción del ejemplar original por la Oficina Internacional**	

PCT (ANEXO - HOJA DE CALCULO DE TASAS)

PCT-58

Original (para **PRESENTACION**) - impreso el 22.11.1999 03:15:47 PM

(Esta hoja no forma parte de la solicitud internacional y no cuenta como una de sus hojas)

0	**Para us de la Oficina receptora únicament**			
0-1	Solicitud internacional No..			
0-2	Sello con la fecha de la Oficina receptora			
0-4	**Formulario - PCT/RO/101 (Anexo) Hoja de cálculo de tasas PCT**			
0-4-1	Preparado usando	PCT-EASY Version 2.90 (actualizado el 15.10.1999)		
0-9	**Referencia al expediente del solicitante o del mandatario**	PCT-58		
2	**Solicitante**	INSTITUTO CIENTIFICO Y TECNOLOGICO DE NAVARRA, S.A., et al.		
12	**Calculo de las tasas prescritas**	importe de la tasa/multiplicador	Importes totales (ESP)	
12-1	Tasa de transmisión T	⇨	10.040	
12-2	Tasa de búsqueda S	⇨	157.235	
12-3	Tasa internacional Tasa de base (30 primeras hojas) b1	68.717		
12-4	Hojas restantes	55		
12-5	Cantidad adicional (X)	1.664		
12-6	Total de la cantidad adicional b2	91.520		
12-7	b1 + b2 = B	160.237		
12-8	Tasas de designación Número de designaciones contenidas en la solicitud internacional	83		
12-9	número de tasas de designación pagaderas (máximo 10)	10		
12-10	Importe de la tasa de designación (X)	15.807		
12-11	Total de las tasas de designación D	158.070		
12-12	Reducción de tasa PCT-EASY R	-21.131		
12-13	Total de la tasa internacional (B+D-R) I	⇨	297.176	
12-14	Tasa por documento de prioridad Número de documentos de prioridad solicitados	1		
12-15	Tasa por documento (X)	4.015		
12-16	Total de la tasa por documento de prioridad P	⇨	4.015	
12-17	**TOTAL DE LAS TASAS PAGADERAS (T+S+I+P)**	⇨	468.466	
12-19	**Modo de pago:**	efectivo		

LISTA DE VALIDACIONES Y OBSERVACIONES

PCT (ANEXO - HOJA DE CALCULO DE TASAS) PCT-58

Original (para **PRESENTACION**) - impreso el 22.11.1999 03:15:47 PM

13-2-3	M nsajes de validación Nombres	Verde? Solicitante 1.: Falta el No. de teléfono
		Verde? Solicitante 1.: Falta el No. de telefacsímile
		Verde? Solicitante 2.: Cuando se indiquen varios nombres de pila se aconseja separarlos mediante comas. Sírvase verificar.
		Amarillo Solicitante 2.: Falta el código postal
		Verde? Solicitante 3.: Cuando se indiquen varios nombres de pila se aconseja separarlos mediante comas. Sírvase verificar.
		Amarillo Solicitante 3.: Falta el código postal
		Amarillo Solicitante 4.: Falta el código postal
		Amarillo Solicitante 5.: Falta el código postal
		Verde? Mandatario 1.: Cuando se indiquen varios nombres de pila se aconseja separarlos mediante comas. Sírvase verificar.
13-2-6	Mensajes de validación Contenido	Verde? No se ha especificado la figura de los dibujos que debe acompañar el resumen. Sírvase verificar.
		Amarillo No se ha indicado la inclusión del documento de acompañamiento "poder separado firmado".

PCT

PCT-58

Original (para **PRESENTACION**) - impreso el 22.11.1999 03:15:47 PM

HOJA DE INFORMACION PCT-EASY

(Unicamente para uso del solicitante, NO someta esta hoja con la solicitud internacional)

LISTA DE VALIDACIONES

	Nombres
Verde?	Solicitante 1.: Falta el No. de teléfono
Verde?	Solicitante 1.: Falta el No. de telefacsímile
Verde?	Solicitante 2.: Cuando se indiquen varios nombres de pila se aconseja separarlos mediante comas. Sírvase verificar.
Amarillo	Solicitante 2.: Falta el código postal
Verde?	Solicitante 3.: Cuando se indiquen varios nombres de pila se aconseja separarlos mediante comas. Sírvase verificar.
Amarillo	Solicitante 3.: Falta el código postal
Amarillo	Solicitante 4.: Falta el código postal
Amarillo	Solicitante 5.: Falta el código postal
Verde?	Mandatario 1.: Cuando se indiquen varios nombres de pila se aconseja separarlos mediante comas. Sírvase verificar.
	Contenido
Verde?	No se ha especificado la figura de los dibujos que debe acompañar el resumen. Sírvase verificar.
Amarillo	No se ha indicado la inclusión del documento de acompañamiento "poder separado firmado".

Antes de presentar la solicitud internacional sírvase verificar atentamente lo siguiente:

-la información contenida en el formulario impreso del petitorio es correcta;
-El recuadro IX del Petitorio ha sido firmado;
-todos los elementos de la solicitud internacional tal como indicados en el recuadro VIII del petitorio han sido adjuntos; y,
-el disquete que contiene el fichero zip de la solicitud internacional PCT-EASY ha sido adjunto y claramente etiquetado "PCT-EASY", con la referencia al expediente del solicitante o del mandatario y el nombre del solicitante.

ATENCION

NO modifique ninguna indicación en el impreso de ordenador del formulario del petitorio. La solicitud PCT-EASY adjunta ha sido cerrada. Si se descubre un error a partir de este momento debe copiar la solicitud presentada como plantilla y efectuar el cambio o corrección en una nueva solicitud (utilizando la solicitud presentada como plantilla). Usted puede crear tal plantilla copiand la solicitud presentada que se encuentra en la carpeta "Formularios enviados" en la carpeta "Nuevos formularios PCT". Abra el nuevo fichero (.0WO) creado en la carpeta "Nuevos formularios PCT", corrija los errores y prosiga de nuevo con el proceso de presentación.

PATENT COOPERATION TREATY

U013446-9

by fax and post

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

Alberto ELZABURU
C/ Miguel Angel, 21
E - 28010 Madrid
ESPAGNE

Fax: 91 319 38 10

ELZABURU Entrada 05.01.01 793602 ACH JV 8.1.01

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)*	29.12.2000
Applicant's or agent's file reference: PCT-58	**REPLY DUE** within 1 month(s) from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/ES99/00375	23/11/1999	24/11/1998

International Patent Classification (IPC) or both national classification and IPC

C07K14/495

Applicant

INST. CIENTIFICO Y TECHN. DE NAVARRA,S.A. et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☒	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain document cited
VII	☒	Certain defects in the international application
VIII	☒	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis. For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 24/03/2001.

Name and mailing address of the international preliminary examining authority:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer / Examiner

Page, M

Formalities officer (incl. extension of time limits)
Sülberg, A
Telephone No. +49 89 2399 7548

I. Basis of the opinion

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*):

Description, pages:

1-47 as originally filed

Claims, No.:

1-18 as originally filed

Drawings, sheets:

1/28-28/28 as originally filed

Sequence listing part of the description, pages:

1-4 (SEQ ID NOs. 1-10), as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:
   ☐ the claims, Nos.:
   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 12 (completely), 13-18 (partially),

because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☒ the claims, or said claims Nos. 12 (completely), 13-18 (partially) are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.
   ☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of inv ntion

1. In response to the invitation (Form PCT/IPEA/405) to restrict or pay additional fees, the applicant has:

☒ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with for the following reasons and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees:

3. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this opinion:

☐ all parts.

☒ the parts relating to claims Nos. 1, 13-18 (partially), 4-10 (completely).

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrialapplicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1, 13-18: NO
Inventive step (IS)	Claims	1, 13-18: NO
Industrial applicability (IA)	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
se separate sheet

The application concerns the provision of peptides that prevent TGFβ1 from binding its receptor. A number of active peptides are presented, and whose sequences are based on the primary structure of the type III TGFβ1 receptor or of endoglin, a TGFβ1-binding protein. The application further seeks protection for mimotopes of the given peptides and expression systems.

Re Item I
Basis of the opinion

Sequence listing pages 1-4 (SEQ ID NOs. 1-10) have been considered.

Re Item III
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The subject matter of claims 12 (completely) and 13-18 (partially) has not been examined with regard to novelty, inventive step and industrial applicablilty because the subject matter of the claims is unclear. The said claims seek protection for mimotopes of peptides. A compound is not sufficiently defined by being a mimotope of a given compound. The subject matter of these claims is therefore not adequately defined in the description and no opinion can be given regarding their novelty, inventiveness or industrial applicability insofar as these claims apply to mimotopes.

Re Item IV
Lack of Unity of Invention

After the invitation to pay additional fees or restrict the application, the Applicant has elected to forgo examination of claims 1, 12-18 (partially), 2, 3 and 11, corresponding to peptide agonists of TGFβ1 based on the polypeptide sequences of TGFβ1 (SEQ ID NOs. 1, 2 and 10).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1) Reference is made to the following documents:
   D1: FR-A1-2720069
   D2: WO-A1-9625178
   D3: HUANG S S ET AL: 'TRANSFORMING GROWTH FACTOR BETA PEPTIDE ANTAGONISTS AND THEIR CONVERSION TO PARTIAL AGONISTS' JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 43, pages 27155-27159

2) **Novelty - Art.33(1) and (2) PCT:**

Claim 1 lacks novelty in light of D2, which discloses peptide fragments of betaglycan (TGFβ1 type III receptor) and endoglin which are capable of binding TGFβ1 and rendering it inactive (D2 page 4 lines 1-5, page 9 line 29 to page 10 line 13 and claims 14 and 15).

Claims 4-10 appear to be novel in light of the cited prior art. The listed peptides have not been previously disclosed.

Claims 13-18 (partially) lack novelty insofar as they are dependent on claim 1. D2 exhaustively discloses methods for the use of peptide agonists of TGFβ1 that are similar to TGFβ1 receptors (e.g. D2 page 3 line 10 to page 4 line 27, page 21 lines 1-16, page 23 line 8 to page 25 line 17, claims 14, 15, 20 and 21, Examples III and IV). The document discloses that these compositions are intended for the treatment of fibrotic diseases, including liver fibrosis (claim 24).

3) **Inventive Step - Art.33(1) and (3) PCT:**

The following comments on inventive step are confined to subject matter which could be acknowledged as being novel, or for which novelty could potentially be restored

as outlined above.

The closest prior art is D2, which provides peptide fragments of betaglycan (type III TGFβ1 receptor) and endoglin that prevent TGFβ1 from binding to the receptor for disease treatment (D2 claims 14, 15, 20 and 24).

In light of the prior art, the technical problem can be regarded as the provision of further betaglycan and endoglin peptides that prevent TGFβ1 from binding to its receptor.

The technical problem is solved by the subject matter of claims 4-10, which provide a number of novel peptides based on the amino acid sequences of these two proteins.

Claims 4-10 (completely) appear to demonstrate inventive step in light of the cited prior art. The document D2 does not disclose any specific sequences for the suggested peptides and does not render the specific sequences obvious.

N.B.: Although claims 13-18 lack novelty and therefore inventive step in light of their dependency on claim 1, it appears that it would be possible to acknowledge novelty and inventive step for the subject matter dependent on claims 4-10 should the said claims be restricted appropriately.

4) **Requirements for any Amendments Art. 34(2)(b) PCT:**

Any information the applicant may wish to submit concerning the subject-matter of the invention, for example further details of its advantages or of the problem it solves, and for which there is no basis in the application as filed, should be confined to the letter of reply and not be incorporated into the application.

In order to facilitate the examination of the conformity of the amended application with the requirements of Article 34(2)(b) PCT, the applicant is requested to clearly identify the amendments carried out, no matter whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application

as filed on which these amendments are based (see also Rule 66.8(a) PCT).

Re Item VII

Certain defects in the international application

a) Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D3 are not mentioned in the description, nor are these documents identified therein.

Re Item VIII

Certain observations on the international application

a) The term "sequences that are identical or *similar* to" in claim 1 renders the scope of the said claim obscure. The subject matter would best be defined through the definition of a percent identity to the sequences of the application for which protection is sought (Article 6 PCT).

b) Claims 15-18 seek protection for a method for manufacturing a peptide of the application using a recombinant expression system. The description does not provide any such systems and the said claims therefore completely lack support and should either be removed (claims 15-17) or ammended to exclude the subject matter (claim 18).

INTERNATIONAL SEARCH REPORT

International application No.
PCT/ ES 99/00375

A. CLASSIFICATION OF SUBJECT MATTER
IPC7 : C07K 14/495, C07K 14/71, A61K 38/18
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC7 : C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CIBEPAT, EPODOC, PAJ, MEDLINE, EMBASE, REGISTRY, CAS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FR 2720069 A1 (I.N.S.E.R.M.), 24 November 1995 (24.11.95), the whole Document	1, 12-18
X	WO 9625178 A1 (The University of Utah) 22 August 1996 (22.08.96), the whole document	1, 12-18
X	WO 9220793 A1 (The Salk Institute for Biological Studies) 26 November 1992 (26.11.92), the whole document	1, 12-18

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot beconsidered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
08 March 2000 (08.03.00)	14 March 2000 (14.03.00)
Name and mailing address of the ISA/S.P.T.O.	Authorized officer Telephone No.

INTERNATI L SEARCH REPORT
Informatic patent family members

International Application No
PCT/ ES 99/00375

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR 2720069 A1	24.11.1995	NONE	
WO 9625178 A1	28.08.1996	AU 4922096 A	04.09.1996
		AU 694621 B	23.07.1998
		CA 2213198 A	22.08.1996
		EP 0809517 A	03.12.1997
		JP 11500128 T T	06.01.1999
		US 5824655 A	20.10.1998
WO 9220793 A1	26.11.1992	AU 1994592 A	30.12.1992
		AU 654724 B	17.11.1994
		CA 2086327 A	11.11.1992
		EP 0542971 A	26.05.1993
		JP 6500574T T	20.01.1994
		US 5885794 A	23.03.1999

INFORME DE BÚSQUEDA INTERNACIONAL

Solicitud internacional nº
PCT/ ES 99/00375

A. CLASIFICACIÓN DEL OBJETO DE LA SOLICITUD

CIP[7] C07K 14/495, C07K 14/71, A61K 38/18
De acuerdo con la Clasificación Internacional de Patentes (CIP) o según la clasificación nacional y la CIP.

B. SECTORES COMPRENDIDOS POR LA BÚSQUEDA

Documentación mínima consultada (sistema de clasificación, seguido de los símbolos de clasificación)

CIP[7] C07K A61K

Otra documentación consultada, además de la documentación mínima, en la medida en que tales documentos formen parte de los sectores comprendidos por la búsqueda

Bases de datos electrónicas consultadas durante la búsqueda internacional (nombre de la base de datos y, si es posible, términos de búsqueda utilizados)

CIBEPAT, EPODOC, PAJ, MEDLINE, EMBASE, REGISTRY, CAS

C. DOCUMENTOS CONSIDERADOS RELEVANTES

Categoría*	Documentos citados, con indicación, si procede, de las partes relevantes	Relevante para las reivindicaciones nº
X	FR 2720069 A1 (I.N.S.E.R.M.), 24.11.1995, todo el documento	1, 12-18
X	WO 9625178 A1 (The University of Utah) 22.08.1996, todo el documento	1, 12-18
X	WO 9220793 A1 (The Salk Institute for Biological Studies) 26.11.1992, todo el documento	1, 12-18

☐ En la continuación del recuadro C se relacionan otros documentos ☒ Los documentos de familia de patentes se indican en el anexo

* Categorías especiales de documentos citados:

"A" documento que define el estado general de la técnica no considerado como particularmente relevante.

"E" solicitud de patente o patente anterior pero publicada en la fecha de presentación internacional o en fecha posterior.

"L" documento que puede plantear dudas sobre una reivindicación de prioridad o que se cita para determinar la fecha de publicación de otra cita o por una razón especial (como la indicada).

"O" documento que se refiere a una divulgación oral, a una utilización, a una exposición o a cualquier otro medio.

"P" documento publicado antes de la fecha de presentación internacional pero con posterioridad a la fecha de prioridad reivindicada.

"T" documento ulterior publicado con posterioridad a la fecha de presentación internacional o de prioridad que no pertenece al estado de la técnica pertinente pero que se cita por permitir la comprensión del principio o teoría que constituye la base de la invención.

"X" documento particularmente relevante; la invención reivindicada no puede considerarse nueva o que implique una actividad inventiva por referencia al documento aisladamente considerado.

"Y" documento particularmente relevante; la invención reivindicada no puede considerarse que implique una actividad inventiva cuando el documento se asocia a otro u otros documentos de la misma naturaleza, cuya combinación resulta evidente para un experto en la materia.

"&" documento que forma parte de la misma familia de patentes.

Fecha en que se ha concluido efectivamente la búsqueda internacional. 08 Marzo 2000 (08.03.2000)	Fecha de expedición del informe de búsqueda internacional 14 MAR 2000 14.03.00
Nombre y dirección postal de la Administración encargada de la búsqueda internacional O.E.P.M. C/Panamá 1, 28071 Madrid, España. nº de fax +34 91 3495304	Funcionario autorizado M. NOVOA SANJURJO nº de teléfono + 34 1 3495552

INFORME DE BÚSQ. .DA INTERNACIONAL
Información relativa a miembros de familias de patentes

S. d internacional nº
PCT/ ES 99/00375

Documento de patente citado en el informe de búsqueda	Fecha de publicación	Miembro(s) de la familia de patentes	Fecha de publicación
FR 2720069 A1	24.11.1995	NINGUNO	
WO 9625178 A1	28.08.1996	AU 4922096 A	04.09.1996
		AU 694621 B	23.07.1998
		CA 2213198 A	22.08.1996
		EP 0809517 A	03.12.1997
		JP 11500128 T T	06.01.1999
		US 5824655 A	20.10.1998
WO 9220793 A1	26.11.1992	AU 1994592 A	30.12.1992
		AU 654724 B	17.11.1994
		CA 2086327 A	11.11.1992
		EP 0542971 A	26.05.1993
		JP 6500574T T	20.01.1994
		US 5885794 A	23.03.1999

PATENT COOPERATION TREATY

U013446-9

by fax and post

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

Alberto ELZABURU
C/ Miguel Angel, 21
E - 28010 Madrid
ESPAGNE
FAX NO: 91 319 38 10

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)* 02.03.01	
Applicant's or agent's file reference PCT-58	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/ES99/00375	23/11/1999	24/11/1998

Applicant
INST. CIENTIFICO Y TECHN. DE NAVARRA,S.A. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Büchler, S Tel.+49 89 2399-8090

Form PCT/IPEA/416 (July 1992)

EL728212738US

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PCT-58		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/ES99/00375	23/11/1999	24/11/1998
International Patent Classification (IPC) or national classification and IPC C07K14/495		
Applicant INST. CIENTIFICO Y TECHN. DE NAVARRA,S.A. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20/06/2000	02.03.01
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Page, M Telephone No. +49 89 2399 7322

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/ES99/00375

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1,2,4-47	as originally filed			
3	as received on	26/01/2001	with letter of	26/01/2001

Claims, No.:

1-15	as received on	26/01/2001	with letter of	26/01/2001

Drawings, sheets:

1/28-28/28 as originally filed

Sequence listing part of the description, pages:

1-4 (SEQ ID NOs. 1-10), as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☒ contained in the international application in written form.
   - ☒ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence

listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)
   see separate sheet

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 9 (completely), 10-15 (partially).

because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☒ the claims, or said claims Nos. 9 (completely), 10-15 (partially) are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

   ☒ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:
   see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1, 13-18 (partially), 4-10 (completely).

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2-8 (completely), 10-15 (partially)
	No:	Claims	
Inventive step (IS)	Yes:	Claims	2-8 (completely), 10-15 (partially)
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	10-15 (partially), 2-8 (completely)
	No:	Claims	

2. Citations and explanations
   see separate sheet

VII. Certain defects in th int rnational application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

The application concerns the provision of peptides that prevent TGFβ1 from binding its receptor. A number of active peptides are presented, and whose sequences are based on the primary structure of the type III TGFβ1 receptor or of endoglin, a TGFβ1-binding protein. The application further seeks protection for mimotopes of the given peptides and expression systems.

Re Item I

Basis of the opinion

The amended **claim 1** submitted on the 26.01.01 was found not to be allowable. The new claim seeks protection for peptides of ≤15 amino acids in length. Such a range is not disclosed in the application as originally filed, as the examples include peptides between 9 and 23 amino acids in length.
New **claims 2-15** were found to conform to the requirements of Article 34(2)(b) PCT. Basis for the claimed length of peptide in claim 1 is considered to be the length of peptides SEQ ID NOs. 3-9, which are all between 9 and 15 amino acids long.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The subject matter of **claims 9 (completely) and 10-15 (partially)** has not been examined with regard to novelty, inventive step and industrial applicability because the subject matter of the claims is unclear. The said claims seek protection for mimotopes of peptides. A compound is not sufficiently defined by being a mimotope (relatively small peptide of undisclosed structure) of a given compound. A small peptide is not adequately disclosed by its function. Being a chemical entity, peptides need to be defined in terms of their chemical structure, i.e. their amino acid sequence. The subject matter of these claims is therefore not adequately defined in the claims or the description and no opinion can be given regarding the novelty, inventiveness or industrial applicability of these claims insofar as they apply to mimotopes.

Re Item IV

Lack of Unity of Invention

After the invitation to pay additional fees or restrict the application, the Applicant has elected to forgo examination of **claims 1, 9-15 (partially)** corresponding to peptide agonists of TGFβ1 based on the polypeptide sequences of TGFβ1. The subject matter examined is confined to peptide agonists of TGFβ1-binding to its receptors that are characterised by being identical or similar to those of natural TGFβ1 receptors.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1) Reference is made to the following documents:
D1: FR-A1-2720069
D2: WO-A1-9625178
D3: HUANG S S ET AL: 'TRANSFORMING GROWTH FACTOR BETA PEPTIDE ANTAGONISTS AND THEIR CONVERSION TO PARTIAL AGONISTS' JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 43, pages 27155- 27159

2) **Novelty - Art.33(1) and (2) PCT**:

Claims 2-8 appear to be novel in light of the cited prior art. The listed peptides have not been previously disclosed.

Claims 10-15 (partially) appear to be novel in light of the cited prior art, insofar as the subject matter is dependent upon claims 2-8.

3) **Inventive Step - Art.33(1) and (3) PCT**:

The following comments on inventive step are confined to subject matter which could

be acknowledged as being novel as outlined above.

The closest prior art is D1, which provides peptide fragments of TGFβ1 that inhibit TGFβ1 activity for therapeutic purposes (D1 page 3 lines 24-28, claims 18-22).

In light of the prior art, the technical problem can be regarded as the provision of further TGFβ1 peptides that prevent TGFβ1 from activating its receptor.

The technical problem is solved by the subject matter of claims 2-8 and 10-15, which provide a number of novel peptides based on the amino acid sequences of these two proteins and their use in manufacturing pharmaceutical compositions.

Claims 2-8 appear to demonstrate inventive step in light of the cited prior art. The document D2 does not disclose any specific sequences for the suggested peptides and does not render the specific sequences obvious.

Claims 10-15 (partially) can also be acknowledged as demonstrating inventive step, insofar as the subject matter is dependent on claims 2-8. D1 provides fragments of TGFβ1 that prevent TGFβ1 from activating the receptor for disease treatment. The difference between the prior art and the application is that the peptides of the application are considerably shorter. The prior art does not teach that the novel peptide sequences provided by the application will also prevent receptor activation.

R Item VII

C rtain defects in the international application

a) Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D3 are not mentioned in the description, nor are these documents identified therein.
N.B.: The replacement sheet 3 submitted on the 26.01.01 was identical to the originally submitted sheet 3.

Re Item VIII

Certain observations on the international application

a) The term "sequences that are identical or similar to" in claim 1 renders the scope of the said claim obscure. The subject matter would best be defined through the definition of a percent identity to the sequences of the application for which protection is sought (Article 6 PCT).

b) Claims 12-15 seek protection for a method for manufacturing a peptide of the application using a recombinant expression system. The description does not provide any such systems and the said claims therefore completely lack support. Even though recombinant expression systems are regarded to be a part of the state of the art, Article 6 PCT states that the claims "shall be fully supported by the description."

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CONFIRMATION BY COURIER

Re: International Application N° PCT/ES99/00375

Reply to the written opinion drawn up by the EPO acting as IPEA

Re Item III: Clarity

We enclose herewith an article published in Internet, wherein the term mimotope is defined as peptide mimics of protein ….and that relates those mimotopes to….many receptor ligands interactions.

Preferred option I: To leave the application as it stands right now in respect of the mimotopes but including the attached article with the definition of the term "mimotope" confined to the application's file wrapper.

Alternative option II: If the examiner would consider that, as a matter of clarification, a definition of the term mimotope should be included, we shall add the aforesaid definition after last paragraph of page 6.

Re Item IV: Unity of invention

A new set of amended claims is enclosed herewith wherein former claims 2,3 and 11 have been removed. The rest of claims have been renumbered and accorded in their new dependencies one with each other (Replacement sheets 48-49).

Re Item V: Novelty and Inventive step

We have amended the drafting of claim 1 to restrict the protection scope sought in view of the prior art. New amended claim 1 as drafted in replacement sheet 48, in our opinion is free of prior art because none of the documents D1-D2 disclose short synthetic peptides $\leq$ 15 amino acids. D3 discloses peptides (SEQ ID NO: 5-10) of less than 15 amino acids but referred to consensus sequences of subdomains of the serin kinase or the tyrosine kinase or to amino acid sequences of an activin receptor.

Basis for that amendment can be found in pages 1-4 of the sequence listing.

By excluding claim 1 from prior art by means of the proposed restriction, the amendment introduced renders, in our view, the whole invention, as now defined by the new set of claims, novel and with inventive step over the prior art, according to our view.

Re Item VII: Relevant background art

New replacement sheet 3 mentions D1-D3 with a brief comment on their disclosures (1).

Re Item VIII: Observations

a) The term similar corresponds to a sequence homology percentage of at least 80%. Should the examiner wish we include that homology percentage in the specification and/or the claims, please let us know.
b) Claims 15-18 are based on routine genetic engineering methods which can be found by any skill person in the art in many scientific books, manual, etc.

Whether the examiner would consider definitions of terms such a: "mimotope" and "... sequences ... similar to", must be included in the description without contravene Art. 28.2 PCT, the applicant respectfully request an additional opportunity to submit the aforesaid amendments under Rule 66.4. PCT.

E L Z A B U R U

Dr. M. Illescas

Enclosures: Replacement sheets: 3, 48 and 49;
Internet record of "J. Mol. Recognit. 2000 Nov-Dec; 13(6): 352-9

(1) WO9625178 disclosed active fragments of TGFβ of 45 amino acids. FR2720069 disclosed the modified amino acid sequence of a TGFβ almost complete, without the N-terminal end of the natural polypeptide, and with changes, mutations or deletions, in the C-terminal end, particularly in a Phe which may be substituted by Ile, Ala or Ser or even being deleted. WO9229793 disclosed amino acid sequences of the TGFβ-receptor either longer than 500 amino acids or, when shorter than 15 amino acids, they are not related to TGFβ or its receptors.

of type I, II and III are the best understood so far (reviewed in Attisano L et al. (1994) Biochim. Biophys. Acta 1222:71-80; Derynck R. (1994) Trends Biochem. Sci. 19:548-553; Yingling et al. (1995) Biochim. Biophys. Acta 1242:115-136). Type IV receptors have also been described (MacKay K. and Danielpour D. (1991) J. Biol. Chem. 266:9907-9911) and type V (Ichijo H. et al. (1991) J. Biol. Chem. 266:22459-22464). It has also been reported that the transmembrane and cytoplasmic domains of endoglin (Cheifetz S et al. (1993) J. Biol. Chem. 267:19027-19030; Bellón T. et al. (1993) Eur. J. Immunol. 23:2340-2345; Yamashita et al. (1995) J. Biol. Chem. 269:1995-2001; Zhang H. et al. (1996) J. Immunol. 156:564-573)) have approximately 70% similarity with the type III receptors, both human and of the rat.

RIII would be the one with the task of binding TGFβ1 and presenting it to RII which in its turn would form a complex with RI (Yamashita et al. (1994) J. Biol. Chem. 269:20172-20178) or to complexes in which various molecules of RI are combined with RII (Weiss G. and Massagué J. (1996) EMBO J 15:276-289). RII-RI interaction would give rise to phosphorylation of RI and subsequent activation of its serine/threonine kinase which would phosphorylate to second messengers like the MADR2 proteins (Macías-Silva M et al., (1996) Cell 87:1215-1224).

(1)

Role of TGFβ1 in hepatic differentiation and regeneration

The effects produced are different depending on the moment of development and on the type of cell.

- Enlargement of the extracellular matrix, on acting upon the liver stellate cells (Ito cells), the principal source of matrix proteins (Mustoe TA et al. (1987) Science 237:1333-1336).

CLAIMS

1.- Peptides that are antagonists of the binding of TGFβ1 to its receptors in the body, characterized by being synthetic peptides with sequences having ≤ 15 amino acids that are identical or similar to those of natural TGFβ1 and/or its receptors.

2.- Active peptide according to Claim 1, characterized in that it has the amino acid sequence SEQ ID NO: 3.

3.- Active peptide according to Claim 1, characterized in that it has the amino acid sequence SEQ ID NO: 4.

4.- Active peptide according to Claim 1, characterized in that it has the amino acid sequence SEQ ID NO: 5.

5.- Active peptide according to Claim 1, characterized in that it has the amino acid sequence SEQ ID NO: 6.

6.- Active peptide according to Claim 1, characterized in that it has the amino acid sequence SEQ ID NO: 7.

7.- Active peptide according to Claim 1, characterized in that it has the amino acid sequence SEQ ID NO: 8.

8.- Active peptide according to Claim 1, characterized in that it has the amino acid sequence SEQ ID NO: 9.

9.- Mimotopes of any of the active peptides of Claims 1 to 8, characterized in that they display an antagonistic effect similar to them, but a longer average life in the body than the latter.

10.- Method of using at least one of the active peptides of Claims 1 to 8 and/or at least one of their mimotopes for manufacturing a composition for application in liver diseases.

11.- Method of using at least one DNA that codes for at least one of the active peptides of Claims 1 to 8 for manufacturing a composition for application in liver

diseases that optionally includes at least one of the mimotopes of the said active peptides.

12.- Method of using at the least one recombinant expression system that codes for at least one of the active peptides of Claims 1 to 8 for manufacturing a composition for application in liver diseases that optionally includes at least one of the mimotopes of the said active peptides.

13.- Method according to Claim 12, characterized in that the recombinant system is a defective adenovirus.

14.- Method according to Claim 12, characterized in that the recombinant system is a plasmid.

15.- Method according to Claims 11 to 14 for application to hepatic fibrosis.

Dr. [redacted] VICTOR.

Entrez PubMed

1: *J Mol Recognit* 2000 Nov-Dec;13(6):352-9

Related Articles, Books, LinkOut

PubMed Services

Mimotopes: realization of an unlikely concept.

Meloen RH, Puijk WC, Slootstra JW

Pepscan Systems BV, Lelystad, The Netherlands.

[Medline record in process]

Related Resources

Theoretically it seems highly unlikely that relatively small peptides could mimic functionally discontinuous epitopes of antigens. Nevertheless various recent reports show this to be the case. Peptide mimics of protein-, polysaccharide- and DNA-epitopes have been shown to be able to replace the native epitope. Moreover, some of them are able to induce, when used in a vaccine, antibodies with the same activity as that of the antibody used as a template. These mimics, called mimotopes, can be used in vaccines and diagnostics and can be developed more or less systematically using solely antibodies and random, semi-random and dedicated peptide arrays or libraries. Furthermore, the mimotope concept which seems to have proven itself for antibody and antigen interaction can be applied equally well to many receptor ligand interactions and thus may form a new generic approach to the development of drugs. Ltd.

PMID: 11114068, UI: 21015667

of type I, II and III are the best understood so far (reviewed in Attisano L et al. (1994) Biochim. Biophys. Acta 1222:71-80; Derynck R. (1994) Trends Biochem. Sci. 19:548-553; Yingling et al. (1995) Biochim. Biophys. Acta 1242:115-136). Type IV receptors have also been described (MacKay K. and Danielpour D. (1991) J. Biol. Chem. 266:9907-9911) and type V (Ichijo H. et al. (1991) J. Biol. Chem. 266:22459-22464). It has also been reported that the transmembrane and cytoplasmic domains of endoglin (Cheifetz S et al. (1993) J. Biol. Chem. 267:19027-19030; Bellón T. et al. (1993) Eur. J. Immunol. 23:2340-2345; Yamashita et al. (1995) J. Biol. Chem. 269:1995-2001; Zhang H. et al. (1996) J. Immunol. 156:564-573)) have approximately 70% similarity with the type III receptors, both human and of the rat.

RIII would be the one with the task of binding TGFβ1 and presenting it to RII which in its turn would form a complex with RI (Yamashita et al. (1994) J. Biol. Chem. 269:20172-20178) or to complexes in which various molecules of RI are combined with RII (Weiss G. and Massagué J. (1996) EMBO J 15:276-289). RII-RI interaction would give rise to phosphorylation of RI and subsequent activation of its serine/threonine kinase which would phosphorylate to second messengers like the MADR2 proteins (Macías-Silva M et al., (1996) Cell 87:1215-1224).

Role of TGFβ1 in hepatic differentiation and regeneration

The effects produced are different depending on the moment of development and on the type of cell.

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CLAIMS

1. Peptides that are antagonists of the binding of TGFβ1 to its receptors in the body, characterized in that they have partial amino acid sequences that are identical or similar to those of TGFβ1 itself and/or its receptors.

2. Active peptide according to Claim 1, characterized in that it has the amino acid sequence SEQ ID NO:1.

3. Active peptide according to Claim 1, characterized in that it has the amino acid sequence SEQ ID NO:2.

4. Active peptide according to Claim 1, characterized in that it has the amino acid sequence SEQ ID NO:3.

5. Active peptide according to Claim 1, characterized in that it has the amino acid sequence SEQ ID NO:4.

6. Active peptide according to Claim 1, characterized in that it has the amino acid sequence SEQ ID NO:5.

7. Active peptide according to Claim 1, characterized in that it has the amino acid sequence SEQ ID NO:6.

8. Active peptide according to Claim 1, characterized in that it has the amino acid sequence SEQ ID NO:7.

9. Active peptide according to Claim 1, characterized in that it has the amino acid sequence SEQ ID NO:8.

10. Active peptide according to Claim 1, characterized in that it has the amino acid sequence SEQ ID NO:9.

11. Active peptide according to Claim 1, characterized in that it has the amino acid sequence SEQ ID NO:10.

12. Mimotopes of any of the active peptides of Claims 1 to 11, characterized in that they display an antagonistic effect similar to them, but a longer average life in the body than the latter.

13. Method of using at least one of the active peptides of Claims 1 to 11 and/or at least one of their mimotopes for manufacturing a composition for application in liver diseases.

14. Method of using at least one DNA that codes for at least one of the active peptides of Claims 1 to 11 for

manufacturing a composition for application in liver diseases that optionally includes at least one of the mimotopes of the said active peptides.

15. Method of using at least one recombinant expression system that codes for at least one of the active peptides of Claims 1 to 11 for manufacturing a composition for application in liver diseases that optionally includes at least one of the mimotopes of the said active peptides.

16. Method according to Claim 15, characterized in that the recombinant system is a defective adenovirus.

17. Method according to Claim 15, characterized in that the recombinant system is a plasmid.

18. Method according to Claims 13 to 17 for application to hepatic fibrosis.